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14. ABSTRACT Intracortical probes can be used to record brain signals to control paralyzed or robotic prosthetic limbs. Unfortunately, this technology is not reliable, likely for the reason that these devices are made of extremely stiff materials – 1 million times stiffer than the surrounding brain tissue. This difference in stiffness is believed to create inflammation which degrades the brain tissue and leads to device failure. While it has been previously proposed that flexible intracortical probes would exhibit an improved tissue response and enhanced device performance, there have been no definitive studies that definitively test this hypothesis. We are developing intracortical probes using shape memory polymers (SMPs): materials which have the capacity to transition from stiff to soft upon implantation. We will tune the degree of stiffness such that we can definitively address a fundamental question which limits progress in the field: Does probe softening improve the surrounding tissue response and recording performance of the device? The short term impact will be on the scientific community through publications and presentations. Over the long term, the core technology has exceptional promise for translation into the clinic. SMP-based probes are compatible with reliable manufacturing practices.					
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## INTRODUCTION

The goal of this research has focused on understanding how a key material property, stiffness, influences the robustness of implantable neuroprosthetic technologies. By bypassing damaged regions of the nervous system, brain machine interfaces (BMIs) offer the promise of reducing the burden of injury, a burden disproportionately borne by veterans, and enabling these injured individuals to live more full and interactive lives. Unfortunately, these devices, which take the form of implantable microelectrode arrays or intracortical probes, do not demonstrate long-term robustness. A major aspect of this issue has been hypothesized to be due to the differential stiffness between the implantable device and surrounding brain tissue. We are leveraging state-of-the-art shape memory polymer (SMP) material science where the degree of material softening can be precisely controlled in order to systematically address the importance of implantable device softening in the brain for robust intracortical probe performance. In addition, the fabrication approaches used to create these test structures take advantage of industrial level manufacturing processes such that promising technology arising from this proposal has the capacity for translation by leveraging standard semiconductor processing techniques.

## KEYWORDS

cyclic voltammetry, cytotoxicity, dynamic mechanical analysis, electrochemical impedance spectroscopy, immunohistochemistry, micromotion, modulus, shape memory polymer, sterilization, insulation

## ACOMPLISHMENTS

The table below lists the specific aims as proposed and the status of the subtasks as identified in the SOW. This report covers the performance relative to Lead Investigators Dr. Pancrazio and Dr. Voit of the University of Texas at Dallas (Site 1) (for review of progress from Site 2, please refer to the companion report from Dr. Capadona from Cleveland VA which is Site 2 below). Based on the timeline, the subtasks that are relevant to this 1<sup>st</sup> year report from Dr. Pancrazio and Voit are highlighted below.

Specific Aim (as specified in proposal)	Timeline	Site 1	Site 2	Status
<b>Specific Aim 1: Quantitatively compare the tissue response evoked by short term and chronic implantation of non-softening, moderately softening, and softening shape memory polymer (SMP)-based intracortical probes.</b>	<b>Months</b>	<b>Lead Investigator(s)</b>	<b>Lead Investigator</b>	<b>% complete</b>
Subtask 1: Fabricate non-functional SMP probes and verify physical and thermo-mechanical properties	1-6	Dr. Voit		100%
Subtask 2: Implant all variants of non-functional SMP probes into motor cortex of rats (165 total)	6-18		Dr. Capadona	
Subtask 3: Harvest tissue from non-functional SMP probes implanted rat motor cortex	12-24		Dr. Capadona	
Subtask 4: Comprehensive immunohistochemical analysis of tissue response for acute and chronic SMP-based intracortical probes	18-30		Dr. Capadona	

Subtask 5: Dissemination of data through publication and presentation	24-36	Drs. Pancrazio & Voit	Dr. Capadona	
Milestone Achieved: Identification of distinctive tissue profiles due to differential modulus of non-functional SMP probes		Drs. Pancrazio & Voit	Dr. Capadona	
Milestone Achieved: Local IRB/IACUC approval	3		Dr. Capadona	
Milestone Achieved: HRPO/ACURO approval	6		Dr. Capadona	
<b>Specific Aim 2: Quantitatively compare the long term recording capability of softening and non-softening SMP-based intracortical probes</b>				
Subtask 1: Fabricate functional SMP probes and verify physical and thermo-mechanical properties	1-9	Drs. Voit & Pancrazio		80%
Subtask 2: Implant all variants of functional SMP probes into motor cortex of rats (80 total)	6-30	Dr. Pancrazio		10%
Subtask 3: Perform bi-weekly recordings of single unit activity and electrochemical impedance spectroscopy using functional SMP probes	6-33	Dr. Pancrazio		0%
Subtask 4: Equivalent circuit modeling from EIS	27-36	Dr. Pancrazio		
Subtask 5: Comprehensive immunohistochemical analysis of tissue response for chronic SMP-based intracortical probes at identical time to non-functional, and at failure.	24-36	Dr. Pancrazio	Dr. Capadona	
Subtask 6: Dissemination of data through publication and presentation	24-36	Drs. Pancrazio & Voit	Dr. Capadona	
Milestone Achieved: Determination of differential device performance as a function of the modulus of SMP probes	30	Drs. Pancrazio & Voit	Dr. Capadona	
Milestone Achieved: Local IRB/IACUC approval	3	Dr. Pancrazio		100% in yr 1
Milestone Achieved: HRPO/ACURO approval	6	Dr. Pancrazio		100% in yr 1

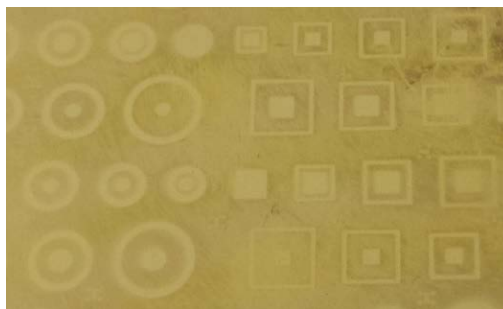
**Milestones:** We are in the process of working through Specific Aim 2 where we have spent the primary focus of the last year working to ensure that we can create robust devices. Last year, we reported that subtask 1 was 70% completed. However, in retrospect, we were not as far along as we thought. Several unanticipated problems arose in moving from a material fabrication effort towards integrated device development. Instead, we believe that this task is well within hand now and should be completed within the next 2-4 months which opens the door for pursuing subtask 2 and 3. We anticipate that there will be a request for a no-cost extension such that the project can complete the chronic implantation studies planned for subtasks 2-6.

**Specific Aim 2, Subtask 1 Progress:** During this last year, we identified 5 major issues that impact the successful completion of this subtask. The following text describes each of these issues and the solutions that we have either identified or are near term. Overall, we have made significant progress and are well-positioned to be successful:

**1. Dielectric Issue:** A common feature of microelectrode devices is the conductive traces which transport electrical signals from the system transducer, or electrode, and directly interact with the complex electronic components necessary to process these physiological signals. In the simplest of terms, the trace is simply an electrically conductive material which is then isolated from other traces and the environment by an electrically insulating material; however, this seemingly simple material configuration can become a source of reliability issues, especially for microelectrode devices. One of the major issues is that the

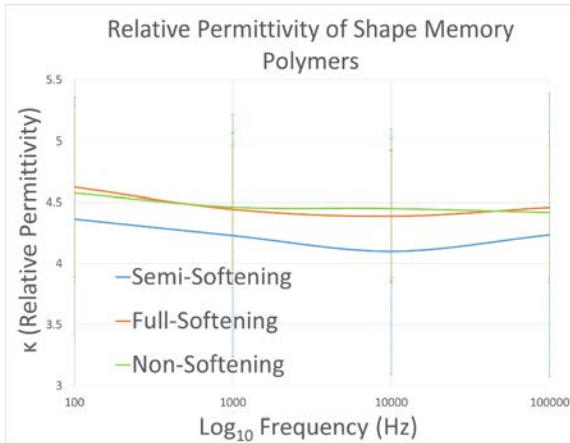
microelectrode device size limits trace component real estate, which thereby decreasing the overall trace area and forcing them closer together. While the decreased size of the trace will increase its resistance, this increase is negligible compared to the impedance of the overall electrode. The critical aspect of the miniaturization is as the thickness of the insulating material decreases, dielectric properties like polarization, electrical breakdown, and resistivity become very important considerations in the microelectrode device design and overall reliability. Failures in the insulation lead to electrical leakage between traces and a loss of signal specificity, while polarization leads to increased parasitic shunt capacitance and increased conductive coupling which leads to cross talk between individual lines.

To fully ensure that our hypothesis is being tested using electrically equivalent and capable probes, we need to fully characterize the SMP material to determine the dielectric properties and to ensure our design will produce similar electrical recording capabilities. Although each of the SMPs developed for this project have similar chemical monomer constituents, their major difference is in the fact that they have an engineered storage modulus at 37 °C in an aqueous environment. One concern is that at the glass temperature of a polymer, relaxation of the molecular bonds leads to a sharp increase in the relative permittivity due to increased polarization, and accordingly, this becomes an increase in the capacitance that develops between trace wires. This increased capacitance will lead to possible effects in the electrical recording equality for the SMP implantable microelectrode devices, especially with the fully softening material. **Figure 1** displays a sample with a maximum of 74 parallel plate capacitors designed to evaluate the dielectric properties consisting of surface and volume resistivity along with relative volume permittivity for each of the SMP materials. The capacitors were designed using the standard techniques established by ASTM International and the Institute for Interconnecting and Packaging Electronics. The results from this study will not only assist in the successful implementation of SMP implantable microelectrode devices to evaluate our general hypothesis, but it can be applied to a wider device biomedical device community with the interest that SMP has garnered.



**Figure 1:** A 22.6  $\mu\text{m}$  thick, fully softening SMP spun onto a gold plated silicon wafer. The pattern seen is the top gold layer which forms the top plate and guard rings for the capacitors which are used to determine resistivity and relative permittivity.

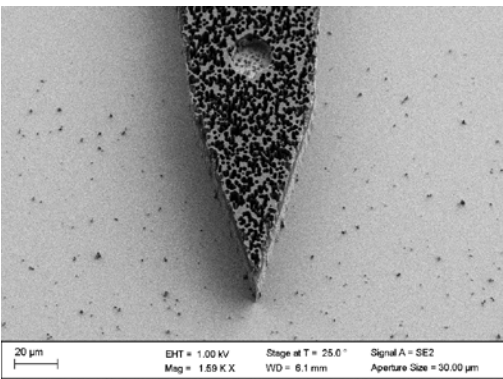
We have completed the initial study on the dielectric properties for the three SMP formulations. Each wafer had at least 50 testable capacitors which were evaluated for relative permittivity between 100 Hz to 100 KHz, once per decade. The application of 90 VDC was used to determine the volume and surface resistivity for the polymers. **Figure 2** displays a graph of the relative permittivity for the SMP materials at room temperature. The relative permittivity of SMP between 4.1 and 4.6 across 100 Hz to 100 KHz indicates that SMP has a polarization similar to materials like silicon dioxide ( $\kappa = 3.7$ ) and other glass compounds ( $\kappa = 3.7 - 10$ ). The SMP polymers have also demonstrated a  $2.0 \times 10^{16} \Omega \cdot \text{cm}$  surface resistivity and  $8.9 \times 10^{14} \Omega \cdot \text{cm}$  volume resistivity. These values were obtained from the native materials at room temperature (22 °C) in air. We are currently performing the same measurements for these values at 37 °C, and evaluating the material in the presence of the PBS electrolyte.



**Figure 2:** Relative permittivity across frequencies from 100 Hz to 100 KHz at room temperature. The fully- and non-softening SMP polymers display a similar relative permittivity, with the semi-softening showing a lower polarization across the frequencies.

ideal for use as the only insulating material for fabricating an electrical trace. However, it may make an ideal material for the fabrication of a capacitor with the higher polarization. This means SMP is ideal for the design of various biomedical sensors and thin film diaphragms. In the previous report, we have discussed the use of Parylene C as the insulation for the trace metal. With a resistivity of  $8.8 \times 10^{16} \Omega\text{cm}$ , and a relative permittivity 3.10 at 1 KHz, it has already been used as an insulation for commercial microelectrode devices, like the Blackrock array and MicroProbes for Life microwires. However, we wanted to only employ only a very thin layer ( $<500 \text{ nm}$ ) in order to provide for the insulation so we could maintaining the physical properties of the SMP materials. The chances of this thin layer failing through pinholes or cracking is quite possible, and this new dielectric information concerning the SMP materials show that it will not provide adequate insulation for an implantable device. With that mind, we will examine the Parylene C layer and ensure that there is minimal chances for pinholes, cracking, or delamination from the SMP or metal layers.

**2. Roughness Issue:** At the end of the last reporting period, we had identified and addressed a problem in the thermomechanical properties of the polymer. Specifically, the curing step, which involves a 1 hr exposure 254 nm UV, was creating an outer crust that did not soften in a manner as the bulk polymer. To address this, we developed an etching step to eliminate the crust and anticipated that we would then be able to progress towards fabricating devices which consist of multiple layers. Unfortunately, fabrication revealed that the surface etch was causing problems in the finalized devices. We observed pitting in outer layers of the devices and it was suspected that the roughness created by the surface etch was resulting in uneven hard mask deposition and subsequent uneven etching (Figure 3). It was determined that maintaining a smooth surface would most likely eliminate these defects; therefore, time was spent finding a new



**Figure 3:** SEM image of pitting observed in top SMP layer. Thanks to Dr. Alexandra Joshi-Imre (UTD) for the image.

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At the conclusion of these measurements, we will be performing accelerated aging protocols by placing the wafers in an oven at  $77^\circ\text{C}$ . The wafers will be removed and a select set of capacitors be monitored to establish the electrical shelf life of electrode devices.

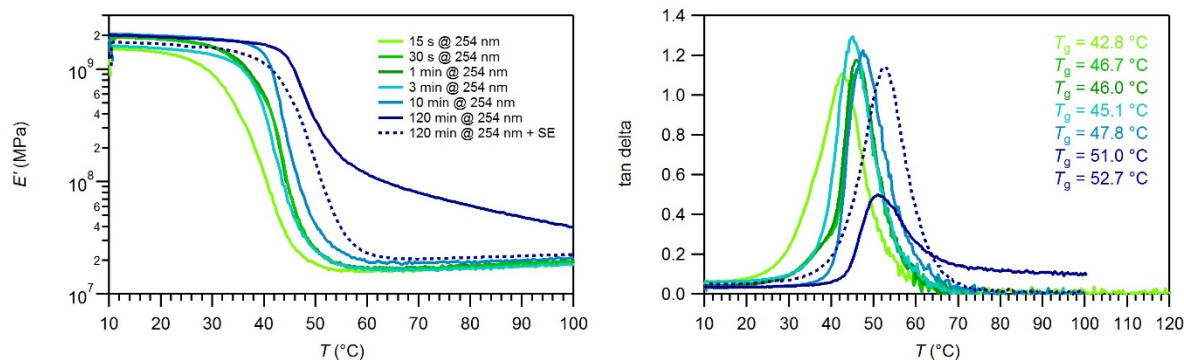
Trace insulation should have a low relative permittivity, optimally as close to the permittivity of free space as is possible, as this will ensure a decrease in parasitic capacitance and capacitive signal transfer between traces. Insulating materials should also possess resistivity of at least  $10^{16} \Omega\text{cm}$  to reduce electrical leakage. The lower value for the resistivity, combined with a relatively high permittivity, suggests that SMP may not be



cure regimen that would not create a heterogeneous surface layer and maintain desirable properties of the SMP. Previously, the SMP was cured at 254nm UV wavelength for 2 hours. Here, we evaluated this curing regimen for the fully softening SMP version along with 5 new curing regimens:

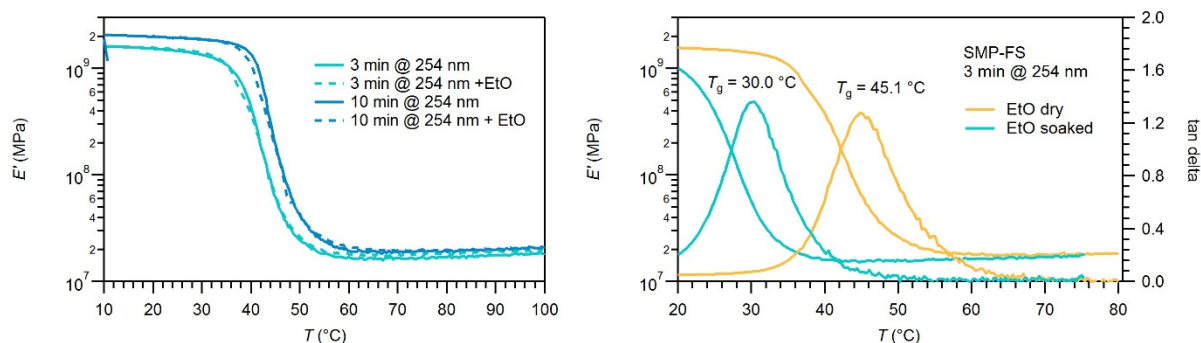
Regimen	Cure Time at 254nm UV Light	Cure Time at 365nm UV Light
1	120 min	none
2	10 min	1 hr
3	3 min	1 hr
4	1 min	1 hr
5	30 s	1 hr
6	15 s	1 hr

Results from Dynamic Mechanical Analysis (DMA) and tan delta, which test the ability of the material to soften as a function of temperature, indicated that cures in regimen 2 and 3 produced thermomechanical properties most closely matched with surface etched SMP (Figure 4).



**Figure 4:** DMA measurements of the fully softening SMP after different curing regimens in comparison to the previously used curing followed by surface etching (SE). Left graphic shows the storage modulus, a measure of stiffness over temperature and the right graphic shows the tangent delta, where the peak gives the glass transition temperature of the polymer.

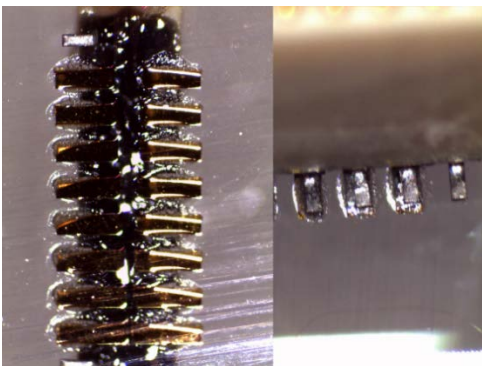
We also verified that sterilization with ethylene oxide (EtO) has no impact on the thermomechanical properties of the SMP, and that the fully softening (FS) SMP is still able to soften over two orders of magnitude upon immersion in PBS at 37 °C (Figure 5).



**Figure 5:** Left: Comparison of DMA measurements of the cure regimen 2 and 3 before and after sterilization with EtO; Right: DMA measurements of the sterilized sample 3 in the dry mode and after soaking for 60 min in PBS at 37 °C.



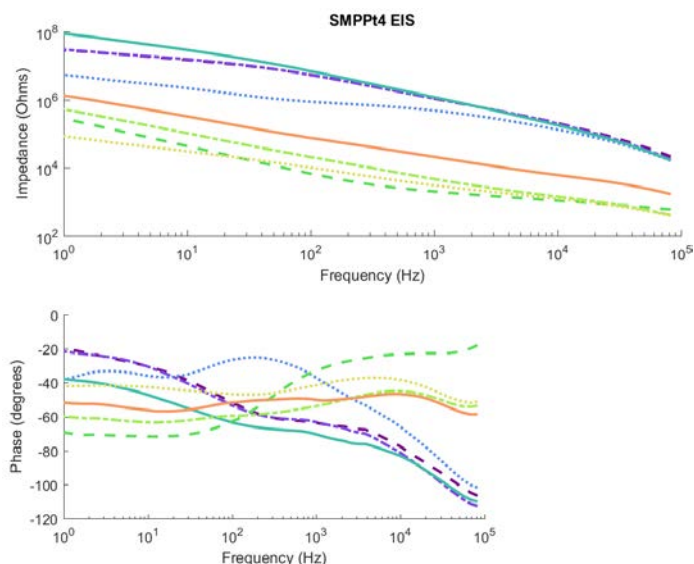
**3. Connectivity Issue:** An additional issue emerged while trying to establish an electrical connection between the microelectrode array to external electronics, specifically with the Omnetics connector necessary for interfacing with all other laboratory devices. Multiple commercial microelectrode systems from companies like NeuroNexus and Blackrock have established the use of common connectors (e.g., Omnetics) among the neuroscience community. These connectors are by necessity extremely small and are usually connected using soldering techniques which rely on alloys that melt at relatively high temperatures, e.g. 188 °C. We have determined that many of the soldering techniques available, including low temperature indium/silver alloy solders, have proved inadequate to provide a consistent and reliable interface between the SMP devices and external connectors. **Figure 6** shows an example of low temperature (~50 °C) 100% In solder which we used with one of our SMP microelectrode devices to connect an Omnetics 18 pin connector. The solder did not flow in



**Figure 6:** An example of an Omnetics connector soldered using reflow on a SMP with a pad consisting of Gold (300nm) / Nickel (300nm) /Gold (300nm). The 100% indium solder paste (Indalloy4) flowed around the edges of the Omnetics pad, but failed to flow between the Omnetics and SMP pads. Damage from solder diffusion is visible in the SMP at the vicinity of the contact pads.

between the pad on the SMP device and the pads on the Omnetics connector, to create an optimal contact. Instead, the solder clustered around the edges of the junction between the two devices, leading to an extremely high impedance junction. An additional problem is that the solder would also diffuse into the SMP material surrounding the pad connection, which would lead to shunting between the electrode traces. At 50 °C, the softening and semi-softening SMP also experience warping which would also lead to a total disconnection between the device pad and the Omnetics pads. We then moved to using conductive epoxies as an alternative solution for creating a connection between the Omnetics connector and the electrode pads. Gold epoxy was used, but proved to be extremely viscous and difficult to apply to the trace pads. Adding a

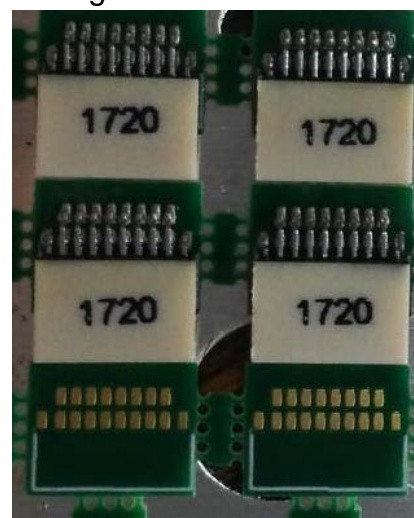
solvent to thin the epoxy would often cause additional damage to the SMP material. And it was discovered that for an optimal curing, the epoxy required high temperature processing which was well above 50 °C. We used silver pastes with much the same results as the gold epoxy. Graphitic epoxy was tried, but possessed extremely low viscosity, often flowing onto the surrounding SMP and creating shunt junctions between the trace pads. We tried a single component silicone epoxy from Masterbond impregnated with silver that was curable at room temperature. The issue with this epoxy was it was cost prohibitive and once the vial was opened, it began to cure and became unusable in 3 days. Overall, the packaging of fabricated devices using solder or conductive epoxy had a maximum usable electrode yield which was approximately 25%. Our experience with NeuroNexus noble metal electrodes with a 144  $\mu\text{m}^2$  surface area shows that they should have an optimal impedance within the range of ~500 K $\Omega$  to 1.5 M $\Omega$ . Our packaged SMP electrode devices had variable impedances which were either greater than 2.5 M $\Omega$  at 1 KHz, or alternately displayed extremely low impedances of less than 10 K $\Omega$  at 1 KHz (**Figure 7**). We needed to find an alternative way to connect the Omnetics connector so the system could be successfully implanted.



**Figure 7:** The recorded impedance from 8 of 16 electrodes from an Omnetics packaged SMP microelectrode. The impedance was obtained using a CH Instruments 608 system through electrochemical impedance spectroscopy (EIS) in 7.4 pH phosphate buffered solution (PBS). The connector was attached to the pads on the microelectrode using a graphitic carbon epoxy. The solid orange line was the only electrode to show characteristic electrochemical activity for a gold electrode of 144  $\mu\text{m}^2$  area. The other electrodes either were either not fully connected, as seen with the blue and purple lines, or they had shunted connections, as seen with the green and dotted orange lines.

the use of a very thin circuit board, with the micro-Ziff connector soldered to one side and an Omnetics connector soldered on the other. The overall small connector aspect ratio is maintained using micro-vias within the circuit board to bridge the connections between the two different connectors. Currently, the Omnetics/ ZIF adapter boards have been fabricated, and some of them have been partially populated as shown in **Figure 8**. The fully populated boards will be finished at the end of October, contingent on the delivery of the remaining Omnetics 90° surface mount connectors which we ordered in August 2017. The new adapter enables us to avoid the warping of the SMP due to high temperature curing above the  $T_g$  of the SMP material, and eliminates the issues experienced from the use of solder or conductive epoxy materials. An additional advantage is that the SMP microelectrode devices, once fabricated and removed from the substrate wafer, can easily and quickly inserted into the adapter board for immediate electrochemical evaluation. Electrical characterization for each electrode will be conducted using EIS and cyclic voltammetry (CV) characterization techniques, with the goal for all electrodes demonstrate a 10% tolerance between all devices. A passing device will be thoroughly rinsed using DI water, inspected using optical microscopy to ensure that there are no obvious defects, and then the Omnetics/ Ziff connector will be encapsulated using Locite brand medical epoxy in order to protect the exposed connector pads. This final package will be placed in a plastic box and then

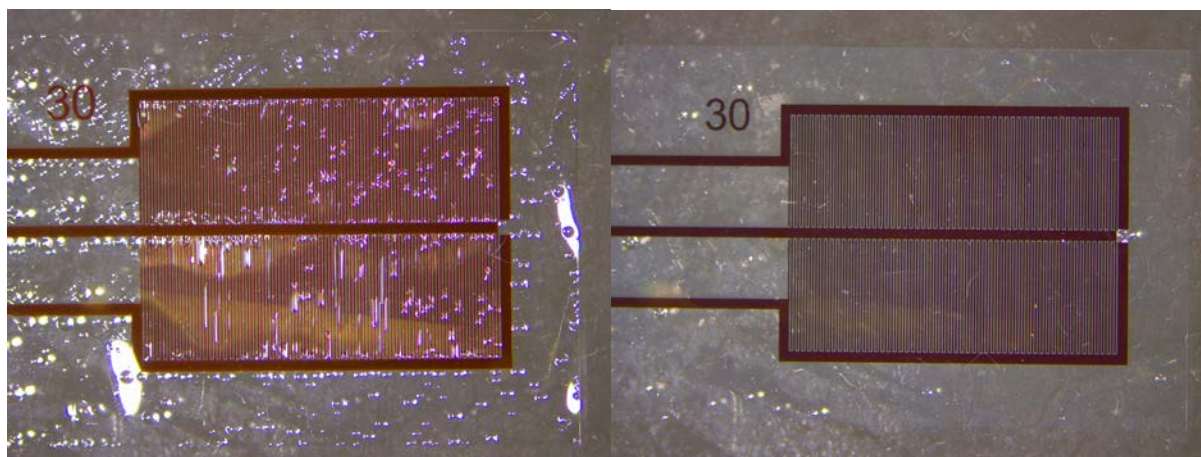
To address this problem, we have designed, and are in the process of fabricating, a novel solution to the connector issue. Zero insertion force (ZIF) connectors are commonly utilized in multiple technological platforms, with a prominent example being within smart phones. They allow high density connection to very thin, flat wire bundles insulated with materials like polyimide, through the application of mechanical force. The ZIF connector should facilitate a reliable connection to the SMP microelectrode device as well, as was shown in an early *in vivo* demonstration published by our group previously (Simon *et al.*, 2017). Since this previous work, ZIF connectors have also become much smaller, and we have located an off-the-shelf solution that has the same width of the Omnetics brand 18 pin connectors. Our design also includes



**Figure 8:** A digital photograph of the completed circuit board with Omnetics connectors soldered on one side and ZIF connectors on the opposite (not imaged) side.

sterilized for subsequent implantation. If the prospective implant falls short of the required electrical characteristics, it will be removed from the ZIF and simply replaced with another device. The new connectors ensure that all of the SMP microelectrode devices are functional, electrically consistent with each other, and also minimizes the loss of Omnetics connectors which have demonstrated a long order turnaround time which will further delay device packaging and implantation.

**4. Layer Adhesion Issue and Solution:** The SMP intracortical probes consist of multiple material layers, including gold traces, the SMP material, and a thin layer of Parylene C to provide uniform dielectric behavior for all devices. We initiated our fabrication of stacked multi-layer devices by first starting with interdigitated electrodes (IDEs), which are often used to assess insulating layer integrity. We determined that the SMP-SMP and SMP-Parylene-C interface is failing as evident from the optical inspection of phosphate buffered saline (PBS) soaked IDE structures. Fluid-filled pockets were observed at the SMP-SMP and SMP-Parylene-C interface implying issues with adhesion in between layers (**Figure 9**). To mitigate this problem, we have started studying various surface treatment methods incorporated into the fabrication process, and preliminary results highlighted significant



**Figure 9:** Pockets of saline solution, shown as bright white spots, formed at the SMP-SMP interface during soak testing in PBS for 5 days at 75 °C. Many pockets were observed when the SMP-SMP interface was treated with low-power oxygen plasma for 30 seconds (image on the left), and few pockets were observed when the plasma treatment was followed by a silane/isopropanol soak (image on the right).

differences between approaches. As a result, we began a detailed investigation of surface treatments considering SMP-SMP, SMP-Parylene-C, Parylene-C-metal, metal-Parylene-C and Parylene-C-SMP interfaces. In a first round of experiments, we are focusing on the polymer interfaces only, and using visual observation of pockets' formation in soak testing as an evaluation method. In a second round of experiments, we will be fabricating IDE structures to include the metal layer, and will be using electrical leakage measurements to assess sample quality.

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standard SMP version that exhibits only moderate softening (SMP6). We consider the use of A-174, a silane based adhesion promoter for Parylene C, to be promising:

Treatment	Description
1	No treatment
2	Oxygen plasma descum
3	Silane A-174 soak
4	O <sub>2</sub> plasma followed by A-174 soak
5	A-174 spin coat
6	O <sub>2</sub> plasma followed by A-174 spin coat

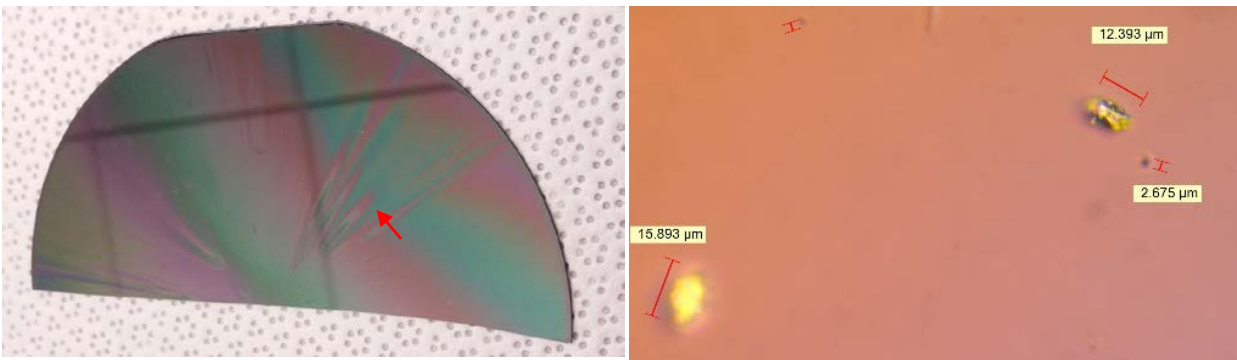
We are using silicon wafers as our substrates and spin coating SMP (29micron) on them. We then clean the SMP surface with deionized water in preparation for the above treatments. One wafer each is allotted to each treatment above. After each treatment is complete, all the wafers go through dehydration bake at 120 °C for 15minutes prior to loading them into Parylene-C coater for a 2 µm Parylene C film deposition. The wafers are then patterned to dry etch the Parylene-C film using DMA ribbons photo mask using O<sub>2</sub> plasma. The photoresist is then stripped off to get the wafers ready for the above surface treatments prior to second SMP coat (5 µm thick). After the second layer of SMP, the wafers are patterned using the same photo mask used above, but with a slight offset to yield areas in the DMA ribbons with both the SMP-SMP and SMP-Parylene-C interface. The SMP is then etched down to the silicon substrate and the ribbons are now released after soaking in DIW. The ribbons will then be used to study adhesion by soaking them in PBS at elevated temperatures and optically inspecting them at different time-points. We expect that the O<sub>2</sub> plasma followed by A-174 soak/spin coat will yield the best results.

**5. Particle contamination issue and solution:** We have observed that SMP substrates, independent of the formulation (non-softening, semi-softening, and fully softening) appear to be contaminated with particles (**Figure 10**). These particles have various shapes and sizes (from 3 to 35 µm) and cause problems during the fabrication of devices in the cleanroom. In addition, these particles may contribute defects of the polymeric barrier layer and increase leakage across insulating layers. We suspected that the particles may come from one or more of the polymer chemical components (monomers or photoinitiator, PI) or get into the uncured solution during the mixing and/or spin coating process. These particles are more obviously visible in thinner (5-7 µm) substrates than in thicker (25-30 µm) substrates, because the majority of the particles is smaller than 15 µm and they tend to sink down to the bottom. We tried to eliminate the contamination by various approaches.

- 1) Since one the components for the SMP is a solid salt (the PI), we ground the salt to see if the particles came from inadequately dissolved PI. It turned out that this procedure could not eliminate the particles. We went one step further and fabricated a substrate completely without PI but still saw particles. Thus the PI was eliminated as particle source.
- 2) We saw particles in all formulations and since the monomer TATATO is the only other component which is part of all SMP's, we wanted to see if we could purify this monomer. We performed column chromatography on the TATATO and separated the monomer from any byproducts and contaminants. After purification we fabricated SMP substrates of different thicknesses but still saw a similar amount of particles.



- 3) We filtered the reactive polymer solution after mixing but before spin coating through a 0.2  $\mu\text{m}$  syringe filter to remove any particles that may be inside this solution. Since the filter was so small, the monomer solution after filtration was full with air bubbles and was not usable for spin coating.

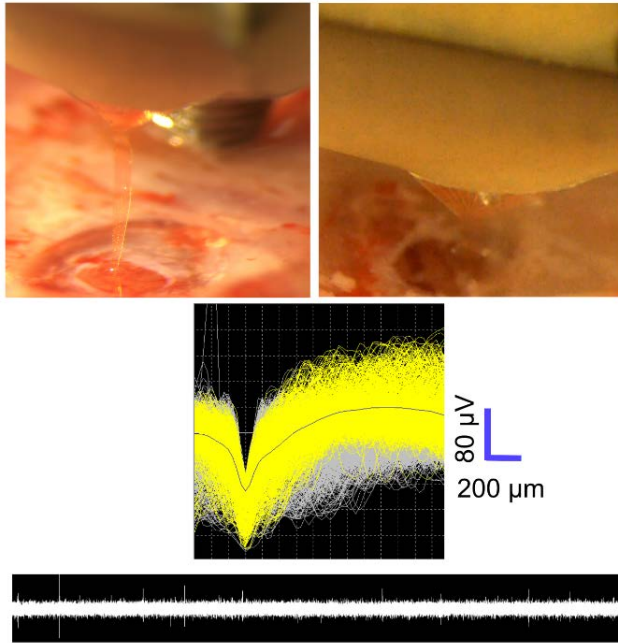


**Figure 10:** Left, Wafer with 5  $\mu\text{m}$  SMP coat showing particles and streaks (arrow) arising from the particles during spin coating. Right, Optical microscope 20x resolution showing different particles in various sizes of the same wafer.

After mixing all components together, the monomer solution becomes reactive and has only a shelf life of 30-45 minutes before it starts to self-polymerize and becomes unusable for spin coating of substrates having reliable properties and thicknesses. Thus, there is only a limited time frame for the usage of this solution and long filtration processes such as a column chromatography are not an option. We are currently looking for other filtration processes which might be applicable for the monomers and the already mixed polymer solution. For the time being, we anticipate that these particle defects will affect device yield and that we can exclude substrates that do not meet optical evaluation. For current device fabrication, all substrates are being investigated visually by the naked eye and with an optical microscope and only those who pass (substrates with very low number of small particles, if any) will go to the next fabrication steps.

Specific Aim 2, Subtasks 2 and 3 Progress: Subtasks 2 and 3 are largely dependent on the completion of the above subtask 1. Subtask 2 involves the implantation of the microelectrode devices fabricated in subtask 1 into the motor cortex of Long-Evans rats, while subtask 3 utilizes the intracortical probes to record single units within the motor cortex of a freely moving animal as well as evaluating the implant through EIS. For these subtasks, the milestones of obtaining the IACUC and ACURO permissions has already been reached and are 100% complete. This subtask progress is currently at 0%, but will follow the implantation and recording schedule with the availability of the new implant devices.

Although there was never a device which had 100% functional electrodes after packaging, we have attempted implantation of partially functional SMP microelectrode devices. We have observed recording of single units within the motor cortex of a Long-Evans rats with one of the devices (**Figure 11**). The softening SMP device showed evidence of a slight bow during the implantation process but did not buckle during the procedure and was successfully implanted to depth. The direct location of the implant was in the motor cortex at 2.5 mm rostral of the coronal suture and 2.5 mm from the sagittal suture on the right hemisphere to a depth of 2 mm. This area has been associated with forelimb and paw control. After implantation, we recorded 10 minutes of electrical signals using an OmniPlex D Neural Data Acquisition System. One of the functional electrodes displayed



**Figure 11:** Digital micrographs obtained from a Zeiss M80 stereo microscope taken during the surgical implantation of an SMP microelectrode. The micrograph on the left shows the microelectrode at the start of the implantation. A slight deflection can be seen, but no buckling occurred. The right image shows the 5 mm device at final implantation depth of 2 mm. A single unit recording was obtained from the initial implantation.

a single unit, which had an average of amplitude of  $76.3 \mu\text{V}_{\text{pp}}$  and a signal to noise ratio of 8.7.

The successful electrical test of the device *in vivo* demonstrates that we are close to solving the majority of the major issues that have prevented the evaluation the effects of material modulus on chronic device reliability and inflammatory response. We are confident that by combining the incorporation of the new SMP curing, the promotion of adhesion chemistry, and the ZIF/Omnetics adapter, we should have electrically equivalent SMP microelectrode implantable devices by the beginning of the New Year. With implantations beginning at that time, the first histological evaluations will begin in May of 2018.

## IMPACT

Brain electrodes are typically fabricated from conductive and insulating materials such as metals and plastics that are inherently stiff, much stiffer than the surrounding brain tissue. The neuroscience community has known that the ability of these devices to record electrical activity is lost after 6 months to 1 year after implantation. The mismatch between the stiff devices and soft brain tissue is believed to be responsible for inflammatory tissue response that plays a major role as a mechanism of failure. Our work aims to test the idea that if we can make a probe that softens in the brain, then the performance of the device would improve. We are capitalizing on a novel material strategy: shape memory polymers. To date, we have made significant progress in identifying the problems related to SMP-based devices and have developed solutions for each. For example, our connector solution is entirely novel and has one of the smallest footprints available for interfacing with a standard Omnetics connector. We are “turning the corner” on the fabrication issues and will be well positioned to create a set of SMP based intracortical probes that differ only by their stiffness and be able to test our study’s central hypothesis that softening probes induce less inflammation through tissue response and exhibit more robust neural recording.

Since we are using fabrication methods that are entirely scalable for manufacturing, our efforts lay the groundwork for eventual translation to the neuroscience research market as well as eventual clinical use. There is widespread need in the neuroscience community interested in basic science questions for devices capable of long-term chronic recording. Moreover, the impact of our work on clinically deployable devices has implications for individuals living with severe neurological deficits where neurotechnology offers a path for restoration. So, when successful, our team will provide an entirely new classes of brain

electrodes that have the potential to impact the neuroscience community to enable the pursuit of scientific questions related to brain circuitry, behavior, and learning.

## CHANGES/ PROBLEMS

As highlighted in the progress report, we have identified a comprehensive set of problems and associated solutions. We overturned every rock such that we do not believe there are any further fabrication related barriers to surmount. In summary, we have made significant progress towards the fabrication of functional intracortical probes comprised of SMP. The delays in Specific Aim 2 subtasks have been marked but can be addressed through a no-cost extension.

## PRODUCTS

### Conferences:

- 2017/04/05: M. Ecker, V. Danda, J. Pancrazio, W. Voit, Effects of sterilization on self-softening thiol-ene/acrylate polymers for bioelectronics, *ACS Meeting*, San Francisco, CA.
- 2017/04/20: M. Ecker, V. Danda, J. Pancrazio, W. Voit, Self-softening shape memory polymers as a scaffold for neural electrodes, *MRS Spring Meeting*, Phoenix, AZ.

## PARTICIPANTS & OTHER COLLABORATING ORGINIZATIONS

**Name:** Joseph J. Pancrazio, PhD

**Project Role:** Principal investigator

**Researcher Identifier:** 0000-0001-8276-3690

**Nearest Person Month Worked:** 12

**Contribution to Project:** project administration, technical supervision of electrochemical testing of intracortical probes and in vivo recordings, supervision of post-doctoral research associate and graduate student, and coordination with the Cleveland VA Site 2.

**Funding Support:** University faculty and administration.

**Name:** Walter Voit, PhD

**Project Role:** Co-investigator

**Researcher Identifier:** 0000-0003-0135-0531

**Nearest Person Month Worked:** 12

**Contribution to Project:** Overseeing shape memory polymer device fabrication, supervision of technical staff in the Cleanroom, and coordination with the PI and the Cleveland VA site.

**Funding Support:** University faculty.

**Name:** Melanie Ecker, PhD

**Project Role:** Post-Doctoral Research Associate

**Researcher Identifier:** 0000-0002-0603-6683

**Nearest Person Month Worked:** 6

**Contribution to Project:** Development and synthesis of new SMP formulations having



various degrees of softening *in vivo*. Thermomechanical characterization of SMP formulations in dry and in soaked states order to verify the softening capabilities. Investigation of the impact of various sterilization methods on the thermomechanical properties and softening on SMP formulations.

**Funding Support:** N/A

**Name:** Christopher L. Frewin, PhD

**Project Role:** Post-Doctoral Research Associate

**Researcher Identifier:** 0000-0002-7591-0629

**Nearest Person Month Worked:** 11

**Contribution to Project:** Responsible for survival surgeries, *in vivo* recordings, electrochemical analysis, Histological analysis, and device design.

**Funding Support:** N/A

**Name:** Alexandra Joshi-Imre, PhD

**Project Role:** Research Assistant Professor

**Researcher Identifier:** 0000-0002-4271-1623

**Nearest Person Month Worked:** 1.7

**Contribution to Project:** Research management; Microfabrication process development; Microscopy; Materials characterization; Yield analysis and Failure analysis.

**Funding Support:** State funded position at the UT Dallas Center for Engineering Innovation.

**Name:** Romil Modi

**Project Role:** Research Engineer

**Researcher Identifier:** 0000-0002-0436-7403

**Nearest Person Month Worked:** 5

**Contribution to Project:** Design and fabrication the SMP implantation devices for the project. Development of the processes required to manufacture a complete device.

**Funding Support:** GSK grant sub-award to Dr. Voit / Qionics

**Name:** Vindhya Reddy Danda

**Project Role:** Research Engineer

**Researcher Identifier:** 0000-0001-8670-8816

**Nearest Person Month Worked:** 10

**Contribution to Project:** Ms. Danda is in charge of fabricating the SMP implantation devices. She also has characterized the devices with DMA and light microscopy.

**Funding Support:** N/A

**Name:** Ms. Lisa Spurgin

**Project Role:** Technician

**Researcher Identifier:** 0000-0001-5240-2085

**Nearest Person Month Worked:** 2

**Contribution to Project:** Fabrication of shape memory polymer substrates

**Funding Support:** N/A

**Name:** Allison Stiller

**Project Role:** Graduate student

**Researcher Identifier:** 0000-0001-6326-890X

**Nearest Person Month Worked:** 12

**Contribution to Project:** Ms. Stiller performs device fabrication, device design, animal surgeries and recording of neural signals.

**Funding Support:** N/A

## **SPECIAL REPORTING REQUIREMENTS**

As required for Collaborative awards, both PIs have submitted a report with tasks for each clearly delineated.